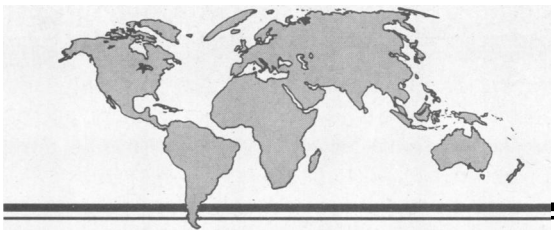

Clinical Manifestations and the Natural History of HIV Infection in Adults

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The clinical expression of infection with the human immunodeficiency virus (HIV) appears increasingly complex. It includes manifestations due to opportunistic diseases, as well as illness directly caused by HIV itself. Neurologic disease may include involvement of the brain, spinal cord and peripheral nerves and is probably directly caused by HIV, as is lymphocytic interstitial pneumonia. The etiology of the chronic diarrhea and a papular pruritic skin eruption associated with HIV infection is unclear. Between 2% and 8% of HIV-infected persons progress to the acquired immunodeficiency syndrome (AIDS) per year, with no apparent decrease in the rate of disease progression over time. A chronically activated state secondary to chronic microbial antigenic exposure may increase both the susceptibility to HIV infection and development of disease. Increased HIV gene expression, followed by persistent antigenemia, appear to be triggering factors in clinical deterioration. The role, if any, of environmental and/or genetic cofactors remains unclear.

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The clinical expression of infection with the human immunodeficiency virus (HIV) appears increasingly complex. It includes manifestations due to opportunistic diseases, as well as illness directly caused by HIV itself. The types of opportunistic infections and neoplasms may vary not only in populations of different geographic origin but also according to the probable way the HIV infection was acquired.

HIV infection may be subdivided into at least four different stages; they are not necessarily present or consecutive events in all patients. These stages include acute illness, the latency phase, persistent generalized lymphadenopathy and AIDS-related complex and AIDS. A precise understanding of the natural history of HIV infection is essential not only for predicting the further course of the AIDS epidemic but also for the development and evaluation of interventions for the prevention and treatment of HIV infection and AIDS.

Clinical Manifestations

Definition of AIDS

The original definition of the acquired immunodeficiency syndrome for surveillance purposes required full documentation of specified opportunistic disease.[1] However, particularly since the widespread availability of HIV serology, a number of new clinical syndromes associated with HIV infection have been recognized. In addition, there has been a growing awareness that physicians may not always want to use often invasive procedures to document opportunistic diseases in patients with AIDS and that adequate diagnostic facilities for opportunistic infections may not be available in many geographic areas, including both industrialized and developing nations. For these reasons and to improve the sensitivity and specificity of the then-prevailing case definition, the Centers for Disease Control have adopted revised AIDS criteria.[2] The major changes in the case definition are the inclusion of HIV encephalopathy and dementia, HIV wasting syndrome and a broader range of specific diseases indicative of AIDS such as certain bacterial infections; the inclusion of AIDS patients whose indicator diseases are diagnosed presumptively, and the elimination of the requirement of the absence of other causes of immunodeficiency.

In 1985 a provisional clinical case definition of AIDS for Africa had already been proposed during a World Health Organization (WHO) Workshop on AIDS in Africa in Bangui, Central African Republic. This case definition was highly specific and moderately sensitive for HIV infection in Kinshasa, Zaire.[3]

Acute Phase

The human immunodeficiency virus disease may occur as early as one week after infection and usually precedes seroconversion, which commonly occurs between 6 and 12 weeks after infection but may take as long as 8 months.

Several studies have now described the clinical manifestations of early HIV disease. Fever, lymphadenopathy, night sweating, headache and cough were all significantly associated with seroconversion. One third to half of patients with seroconversion report at least one of these symptoms (Table 1).[4,5] Seroconversion may also be associated with severe illness, particularly acute encephalopathy.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
HIV = human immunodeficiency virus
PGL = persistent generalized lymphadenopathy
WHO = World Health Organization

Persistent Generalized Lymphadenopathy and AIDS-Related Complex

Persistent generalized lymphadenopathy (PGL) is defined when a patient with HIV infection has lymph nodes of greater than 1 cm in diameter involving two or more extrainguinal sites of at least three months' duration and in the absence of any current illness or drug use known to cause lymphadenopathy. About a third of patients with PGL are asymptomatic. Lymphadenopathy may slowly regress in size during the course of the disease. Systematic performance of lymph node biopsies in HIV-infected persons is not recommended but is indicated when lymph nodes are abnormally large, have an unusual consistency, when there is marked unilateral enlargement or in the presence of a fever of unknown origin.

Patients with AIDS-related complex (ARC) show symptoms, signs and immunologic defects similar to those of AIDS patients, but their symptoms and immunologic abnormalities are less severe. In contrast with AIDS patients, neither opportunistic infection nor malignant lesions can be diagnosed in ARC patients.

Signs and symptoms in ARC patients include weight loss, malaise, fatigue and lethargy, anorexia, abdominal discomfort, diarrhea, fever, night sweating, headache, itching, amenorrhea, lymphadenopathy and splenomegaly. These symptoms and signs are frequently intermittent. Weight loss is found in all patients and is generally progressive. Thrombocytopenia ($<50{,}000$ per μl) develops in approximately 10% of patients and is also often transient.

Many ARC patients have mucocutaneous lesions, and recognition of such skin manifestations can lead to an early diagnosis of AIDS or ARC. Skin manifestations include mainly varicella zoster, seborrheic dermatitis, recurrent and persistent orolabial and genital herpes, molluscum contagiosum, oral candidiasis and oral hairy leucoplakia. A generalized papular pruritic eruption (prurigo) is found in approximately 20% of African patients with HIV infection and frequently starts in an early stage of the disease. The cause is unknown.

Persistent diarrhea is one of the major complaints in patients with ARC or AIDS. Though intestinal parasites such as *Cryptosporidium* species and *Isospora belli* can be identified in 5% to 25% of HIV-infected patients with chronic diarrhea, in most patients no specific cause for the diarrhea is found.

AIDS

AIDS represents the most severe stage of the clinical spectrum of HIV infection. It is characterized by the presence of opportunistic infections and tumors as a result of a profound cellular immunodeficiency. The types of opportunistic infections depend largely on the past exposure of the host to microbial agents. This may explain the differences in frequency of certain opportunistic infections among African and American or European patients with AIDS.[6-11] Thus, *Pneumocystis carinii* pneumonia is by far the most common opportunistic infection in Americans and Europeans but is less frequently found in African patients. In contrast, the gastrointestinal system is a major site of infection in Africans with HIV disease, possibly because of a high exposure to enteric microbial agents. Table 2 shows the relative frequency of the most common opportunistic infections and of Kaposi's sarcoma.

The same signs and symptoms described for ARC patients occur in patients with AIDS but the manifestations become more pronounced. In addition, symptoms caused by opportunistic infections and malignant lesions are found. They will not be discussed here.

An increasing number of neurologic abnormalities are being documented in patients with HIV infections. These neurologic symptoms may be the initial manifestation of HIV disease and are often atypical in presentation. Prolonged headache in a person with HIV infection should always be an indication for a thorough neurologic investigation.

Central nervous system involvement may be directly due to HIV infection or to a variety of opportunistic infections. Neurologic disorders that are probably caused by HIV itself include encephalitis with progressive presenile dementia, acute and chronic meningitis, vacuolar myelopathy, peripheral neuropathy and polymyositis. Other causes of neurologic manifestations in patients with HIV infection include cryptococcal meningitis, cerebral toxoplasmosis, lymphoma of the brain, papovavirus infection, herpes simplex encephalitis,

TABLE 1.—*Clinical Manifestations of Early HIV Disease*

	% of Seroconverters With Symptom	
	Fox and Co-workers N=22*	*Coutinho and Colleagues† N=40*
Pharyngitis	23	...
Coughing	...	25‡
Skin rash	14	15
Fatigue	23	17
Diarrhea	14	5
Fever	23‡	42‡
Lymphadenopathy	36‡	7.5
Night sweat	18‡	10
Headache	23‡	...
Nausea/vomiting	14	7.5

*From Fox, Eldred, Fuchs.[4]
†From Coutinho et al.[5]
‡$P<.05$ as compared to seronegative controls.

TABLE 2.—*Opportunistic Diseases in Different Patient Groups With AIDS**

	With Disease (%)				
		Haitians		Africans	
Opportunistic Disease	*Americans*	*USA*	*Haiti*	*Europe*	*Zaire*
Pneumocystis carinii pneumonia	61	42	20	25	17
Candidal esophagitis	10	51	67	23	17
Diarrhea >1 month					
with *Cryptosporidium*	3	3	5	9	6
with *Isospora belli*	NA	10	NA	4	1
Cryptococcosis	6	10	3	30	5
Herpetic ulceration >1 month	4	17	8	25	3
Cerebral toxoplasmosis	3	27	3	18	NA
Tuberculosis	NA	52	24	12	13
Atypical mycobacteria	4	4	NA	8	NA
Generalized CMV infection	5	13	10	25	NA
Progressive multifocal leukoencephalitis	0.6	1	NA	2	NA
Kaposi's sarcoma	26	12	26	21	4

CMV=cytomegalovirus, NA=not available

*Data from Peterman,[6] Pitchenik,[7] Pape,[8] Sonnet,[9] Colebunders,[10] Katlama,[11] et al.

TABLE 3.—*Development of AIDS in HIV-Antibody-Positive Adults in Selected Studies*

Patient Category	Location	Investigators	No. Studied	Months of Follow up (mean or median)	No. of AIDS Cases per 100 Persons per Year
Homosexual men	San Francisco	Hessal and co-workers[17]	63	72	5.0
	New York City	Polk and others[19]	165	18	4.0
	Multicenter AIDS Cohort Study, USA	Polk and others[19]	1,835	15	2.6
	London, UK	Weber and colleagues[20]	33	36	4.0
	Amsterdam, The Netherlands	De Wolf et al[21]	198	21	4.3
IV drug abusers	Queens, NY	Goedert and co-workers[22]	24	36	1.4
	Bronx, NY	Selwyn et al[23]	163	15	3.9
Blood recipients	USA	Ward and others[24]	54	46	2.4
Hemophiliacs	Hershey, Pa	Goedert and co-workers[22]	40	36	4.2
Heterosexual men and women	Nairobi, Kenya	Plummer and colleagues[25]	535	12	5.7
	Kinshasa, Zaire	Ngaly and others[26]	44	24	2.3

IV=intravenous

infection with cytomegalovirus, tuberculous and candidal meningitis and abscesses.

The most common neurologic disorder is a subacute encephalopathy characterized by progressive behavior changes associated with dementia. This "AIDS encephalopathy" or "AIDS dementia" occurs in approximately one third of AIDS patients. The onset is usually insidious, and cognitive dysfunction predominates initially. Common early motor signs include tremor and slowness, and the course is usually progressive towards severe dementia. Mutism, incontinence and paraplegia may develop in the end stage. A mild pleocytosis, an increased protein concentration and a low glucose concentration are often found upon examination of the cerebrospinal fluid.

Natural History of HIV Infection

Acquisition of Infection by Sexual Intercourse

HIV has now been isolated from virtually all bodily secretions and excretions that have been cultured, but there is no firm evidence as yet that body fluids other than blood, semen, cervicovaginal secretions and perhaps breast milk can transmit the virus. It has still not been unequivocally established in which form HIV is transmitted. However, other animal lentiviruses are transmitted via cell-bound virus inside monocytes and macrophages, and this is probably also the case with HIV. It also appears that HIV can only be isolated from semen, saliva and cervical secretions containing cells and not from cell-free filtrates, suggesting that HIV is cell bound in these secretions.

Though the present data on factors enhancing sexual transmission of HIV are incomplete, some patterns are emerging from studies in both homosexual men and heterosexuals. Genital trauma clearly facilitates sexual transmission of HIV. Thus, it has now been well established in several studies that receptive anal intercourse is the major risk factor for HIV acquisition in gay men. In addition, rectal bleeding during or after intercourse and the use of an enema or douche before sex are risk factors for HIV infection in homosexual men. Similarly, among female prostitutes in Zaire, introducing products or objects into the vagina was associated with HIV seropositivity.[12] Finally, studies in Africa have suggested that genital ulcers are significant risk factors for heterosexual acquisition of HIV.[13] If transmission of HIV infection is more efficient in the presence of genital ulcerations, control of sexually transmitted diseases may play an important role in the indirect control of the spread of HIV infection in some populations.

A second major factor determining infectivity appears to be the stage of infection, probably because of a higher virus expression associated with disease progression. Thus, a female sex partner of an HIV-infected hemophiliac was more likely to be infected when her partner had a low concentration of T helper cells.[14] Such an association between infectivity and duration of infection and low CD 4^+ cell counts was also observed in studies on congenital transmission of HIV infection in Africa.[15,16]

Progression of Disease

After a variable period of time some persons progress to HIV-related disease. Table 3 gives annual progression rates to AIDS in seropositive adults belonging to five different patient categories, showing that per year AIDS develops in approximately 2% to 5% of HIV-infected persons, regardless, apparently, of the route of infection or the life-style.[17-26] In the San Francisco cohort of gay men, which has had the longest observation time, 35% of seropositive men progressed to AIDS nearly seven years after the infection.[18] Patients with PGL or ARC are at increased risk for AIDS, with annual progression rates to AIDS of 6% to 20%. The risk for AIDS apparently does not decrease with the duration of infection.

Why does AIDS develop in some infected persons within five years while others remain healthy? This is a basic question in many infectious diseases, and we tend to forget that the answer is unknown for virtually all.

The respective ongoing cohort studies have come up with a spectrum of risk factors for the development of AIDS. A consistent predictor of clinical deterioration is a low concentration of T helper lymphocytes (OKT 4^+, CD 4^+, Leu $3a^+$ cells). Thus, in one study in Los Angeles, 5% of gay men who had ≥ 500 CD 4^+ cells per μl at enrollment in a study progressed to AIDS, as compared with 50% of men with less than 100 such cells per μl.[27] Additional indicators suggesting a poor prognosis include oral candidiasis, lymphopenia, an increased erythrocyte sedimentation rate, hemoglobin levels below 13 grams per dl, decreased antigen-stimulated lymphocyte proliferation, reduced gamma interferon generation, impairment of the specific cellular response to HIV and the presence of antilymphocyte antibodies.

Investigators in Europe have now documented a specific loss of IgG antibodies against the *gag* gene products of HIV

during clinical progression of HIV infection. Both the prevalence and the concentration of antibodies to the p24 core protein are decreased among patients with AIDS, as compared with asymptomatic HIV-seropositive men.[20,28] In contrast, antibody against the viral envelope glycoprotein remains stable throughout the course of disease. Loss of antibody inhibitor to reverse transcriptase activity appears also to precede the development of AIDS.[29]

The decline in anti-p24 antibodies is probably secondary to increased viral expression. Lange and Goudsmit showed that the decrease in antibody reactivity to the major HIV core protein is due to clearance of these antibodies by excessively produced viral antigen, as evidenced by studies on circulating immune complexes.[30] A drastic decrease of CD 4^+ lymphocytes accompanying a significant increase of free viral antigen concentration seems to be the initial event in clinical deterioration.[21]

Prospective studies suggest the following pattern for free HIV antigen and antibody to p24: After an initial antigenemia preceding seroconversion, there is a variable period without detectable free HIV antigen (however, HIV can still be demonstrated in the T-helper lymphocytes); when anti-p24 antibodies decline, the free viral antigen becomes detectable again, which may herald the onset of AIDS.[10,21,28,30] Individuals with persistent antigenemia following infection are at a significantly increased risk for AIDS.

A reasonable conclusion from several studies is that the primary pathogenic mechanism in serious HIV disease appears to be enhanced expression of viral genes following lymphocyte activation. There is some experimental support for a role of cofactors in the replication and dissemination of HIV. Thus, proliferating CD 4^+ cells are more susceptible to productive infection with HIV in vitro than nonproliferating cells; mononuclear cells activated by tetanus toxoid are 10 to 100 times more susceptible to viral replication[31]; coinfection of cells by HIV and DNA viruses such as herpes simplex and varicella zoster can reactivate transcription of latent HIV by *tat*-like protein. These data suggest that both soluble antigen and DNA viruses may also serve as cofactors in vivo in the development of clinical AIDS. This hypothesis is supported by the observation by Weber and colleagues that interfering sexually transmitted diseases may precipitate clinical deterioration in HIV-seropositive gay men.[32] The data on cofactors are still inconclusive, however, and epidemiologic studies on the role of other infectious diseases are extremely complex. This is also true about the role of other environmental factors such as amyl nitrite use, which has been linked to Kaposi's sarcoma.

An alternative model for the pathogenesis of clinical AIDS is a more direct role for the infecting HIV virus itself. Quantitative differences in in vitro virulence for cells have been reported and correlated with clinical severity of the infection, suggesting the existence of differences in pathogenicity among HIV strains.[33]

Finally, genetic factors in the host may determine both susceptibility to infection and clinical progression patterns. Both group-specific component and different HLA antigens have been implicated in disease expression.[34,35] All these findings require confirmation among persons of diverse geographic and ethnic backgrounds.

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